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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/628,225	07/28/2000	William W. Bachovchin	TUU-P01-006	3405

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EXAMINER	
RUSSEL, JEFFREY E	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 11/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,225	BACHOVCHIN ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-42 and 46-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-42 and 46-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The disclosure is objected to because of the following informalities: The claim for priority inserted by the amendment filed July 24, 2002 must be deleted. Appropriate correction is required.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no original disclosure of the cause of the glucose intolerance recited in instant claim 42. Applicants cite to page 51, line 6, of the specification as support for the amended claim limitation. However, the examiner has not been able to locate a copy of the cited article in order to determine whether or not it supports the claim limitation. (Applicants are requested to check the citation for this article, because the journal "Gastroenterology" lists Volumes 112 and 113, rather than Volume 35, as occurring in 1997.) Further, the citation in the specification is limited to mice, and there is no indication that a GLP-1 receptor gene deletion or disruption exists in glucose intolerant animals in general. Finally, it is not clear, from the brief summary of the article given in the specification, that the article supports both deletion and disruption of the gene encoding the receptor. In general, disclosure of a species (e.g., just mice, or just gene deletion, or just gene disruption) does not constitute adequate written descriptive support for newly presented claims drawn to a genus encompassing the species.

4. Claims 53, 65, and 66 are objected to because of the following informalities: To the extent that claim 53 is dependent upon claims 38, 39, or 40, it is redundant to these claims which

have been amended to require oral administration. It is suggested that claim 53 be amended so that it only depends upon claim 41. At claim 65 (page 15, line 13), "or" should be inserted before the last chemical structure in the line. In the definition of R_6 that was present in claim 66 and was deleted in the amendment filed September 25, 2003, the structural formulas were not struck through. Appropriate correction is required.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 38-42 and 46-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 and 16-40 of copending Application No. 09/601,432. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '432 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 38-42 and 46-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-132 of copending Application No. 10/190,267. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the claims of the '267 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. The effective filing date of instant claims 38-41 and 46-68 is deemed to be February 2, 1998, the filing date of provisional application 60/073,409. Instant claims 38-41 and 46-68 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the parent provisional application because the parent provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention. Accordingly, the Deacon et al article (Diabetes, Vol. 47, pages 764-769) and the WO Patent Application 98/25644 are not available as prior art against these claims. (Drucker, U.S. Patent No. 5,952,301, in the same patent family as the WO Patent Application '644, is not applied against the instant claims because Drucker does not contain any disclosure concerning the use of dipeptidylpeptidase inhibitors.)

9. Claims 38, 39, 41, 44-63, 65, 66, and 68 are rejected under 35 U.S.C. 103(a) as being obvious over the Balkan et al abstract (Diabetologia, Suppl. 40, A131 Abstract) in view of the WO Patent Application 93/08259 and further in view of Efendic et al (U.S. Patent No. 5,631,224). The Balkan et al abstract teaches improving the glucose tolerance of insulin resistant, glucose intolerant, obese Zucker rats by administering the DPP-IV inhibitor SDZ 272-070 (i.e. valine pyrrolidide). The Balkan et al abstract does not disclose the use of DPIV inhibitors having a Ki and an EC_{50} as recited in claims 38, 39, and 47-50, having oral activity, or having the structure recited in instant claims 54-63, 65, and 66. The WO Patent Application '259 teaches inhibiting the enzymatic activity of DPIV in a mammal by administering a peptide

compound. The peptides compounds are proteolyzed by DPIV in vivo until a C-terminal dipeptide portion remains, which acts as an inhibitor of DPIV. The peptide compound is more stable in vivo than the C-terminal dipeptide portion. If the C-terminal dipeptide portion is chosen to be a dipeptide prolyl-boronic acid, then a potent and highly specific inhibitor having a Ki in the nanomolar range is ultimately released in vivo. Tetrapeptides comprising Ala-boroPro and Pro-boroPro as the C-terminal dipeptide portions are taught. As an alternative to the boroPro group, trifluoroalkyl ketone groups are taught. Administration can be oral, and administration amounts range from 1-500 mg/kg/day. See, e.g., page 2, lines 15-32; page 3, line 1 - page 7, line 16; page 14, lines 10-12; page 14, line 34 - page 15, line 16; and page 21, lines 15 and 29-30. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the DPIV inhibitors of the WO Patent Application '259 in the method of the Balkan et al abstract because the DPIV inhibitors of the WO Patent Application '259 have the advantage of having a low Ki and of having chemical stability, which would permit the use of smaller dosages of the active agent, because the DPIV inhibitors of the WO Patent Application '259 are described as being generally useful as inhibitors of DPIV-mediated processes (see, e.g., page 6, lines 4-10) and the method of the Balkan et al abstract operates via a DPIV-mediated process, and because the DPIV inhibitors of the WO Patent Application '259 can be administered orally, which is a more convenient and acceptable method of administration for the patient. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to choose DPIV inhibitors from the WO Patent Application '259 for use in the method of the Balkan et al abstract so as to maximize their effectiveness in treating the intended disease and to minimize their unintended side effects, e.g., so as to minimize their EC_{50} for inhibiting glucose

intolerance and to maximize their EC_{50} for causing immunosuppression. The Balkan et al abstract teaches that administration of its DPP-IV inhibitor may be a useful tool in the treatment of NIDDM, but does not explicitly teach administering a DPP-IV inhibitor to treat Type II diabetes. Efendic et al teach that diabetes is characterized by impaired glucose metabolism manifesting itself among other things by elevated blood glucose levels, i.e. that diabetic patients are glucose intolerant (see column 1, lines 19-21), and teach the administration of GLP-1 in order to treat type II diabetes (see, e.g., column 2, lines 37-49, and column 4, lines 47-67). It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to treat Type II diabetes using a DPP-IV inhibitor suggested by the Balkan et al abstract as modified above by the WO Patent Application '259 to treat Type II diabetes, because the Balkan et al abstract disclose that this may be a viable approach to the management of diabetes, because the Balkan et al abstract's rat model is predictive of in vivo success in humans due to their resemblance to humans in terms of physiology, and because Efendic et al confirm that GLP-1 is useful in the treatment of Type II diabetes. The WO Patent Application '259 does not teach administering its DPIV inhibitors in a single dose. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal dosage schedules for the method of the Balkan et al abstract as modified above by the WO Patent Application '259 and Efendic et al, because dosage schedules are routinely determined and optimized in the pharmaceutical arts, and because it is desirable to minimize the number of administrations which are necessary for patient convenience and patient compliance.

10. Claims 38-40, 46-53, and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by Villhauer (U.S. Patent No. 6,011,055). Villhauer teaches treating non-insulin-dependent

diabetes, i.e. Type II diabetes, and increasing glucose tolerance by administering a DPIV inhibitor having the same structure as Applicants' page 9, line 7 - page 11, line 10. The inhibitors improve early insulin response to oral glucose challenges. Oral administration of the inhibitors is taught. Daily amounts preferably range from 1-100 mg, and oral administration can be 1-3 times/day. See, e.g., the Abstract; column 9, lines 48-65; and column 10, lines 28-42. With respect to instant claims 38-40 and 47-50, in view of the similarity in structure and function between the DPIV inhibitor of Villhauer and Applicants' disclosed DPIV inhibitors, the EC50's and Ki for the DPIV inhibitors of Villhauer will inherently be the same as is recited in instant claims 38-40 and 47-50. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitors of Villhauer and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than the DPIV inhibitors of Villhauer. With respect to instant claim 40, because the same active agents are being administered to the same animals according to the same method steps, inherently peptide hormone metabolism will be modified to the same extent in the method of Villhauer as is claimed by Applicants.

11. Claims 38-40, 44-53, and 68 are rejected under 35 U.S.C. 103(a) as being obvious over the German Patent 196 16 486. The German Patent '486 teaches using DP IV inhibitors to inhibit degradation of gastric inhibitory peptides and glucagon-like peptides, which effect can be used to reduce blood sugar levels and to treat diabetes mellitus. Inhibitors include alanyl pyrrolidide, isoleucyl thiazolidide, and N-valyl prolyl, O-benzoyl hydroxyl amine, and they can be administered orally. See, e.g., pages 1-2; page 10, line 21 - page 11, line 1; and page 11, line 15; of the attached translation. In view of the similarity in structure and function between the

DPIV inhibitors of the German Patent '486 and Applicants' disclosed and claimed DP IV inhibitors, the EC_{50} and K_i values for the DP IV inhibitors of the German Patent '486 will inherently be the same as those recited in the instant claims. Sufficient evidence of similarity is deemed to be present between the DP IV inhibitors of the German Patent '486 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than those of the German Patent '486. The German Patent '486 does not teach administering its DPIV inhibitors in a single dose in amounts less than 2000 mg. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal dosages and dosage schedules for the method of the German Patent '486 because dosage schedules are routinely determined and optimized in the pharmaceutical arts, and because it is desirable to minimize the number of administrations which are necessary for patient convenience and patient compliance.

12. Applicant's arguments filed September 25, 2003 have been fully considered but they are not persuasive.

The rejection under 35 U.S.C. 112, first paragraph, is maintained. It should be noted that the basis for the rejection is lack of written description, not lack of enablement. Much of Applicants' argument is directed towards the latter. The Medline citation attached to Applicants' response shows that the correct name of the journal in which the Gallwitz et al article is "Zeitschrift fur Gastroenterologie". The citation in the specification is either incorrect or is at best incomplete. Without an accurate citation, the specification's reference to the Gallwitz et al article can not be relied upon as support for the claimed subject matter of instant claim 42. In any event, the limited disclosures of the Gallwitz et al article (as summarized by Applicants) and

of Applicants' Figure 4 do not provide written descriptive support for the broader claim language. The disclosure of gene disruption does not support the claim recitation of gene deletion, and the disclosure of mice with a GLP-1 gene defect does not provide support for all animals with GLP-1 gene defects.

The objection to claim 65 is maintained. The objection indicated that the word "or" should be inserted before the last chemical structure in the line. The examiner agrees that the word "or" which occurs after the last chemical structure in the line is appropriate, but this is not the basis of the objection.

The obviousness rejection set forth in paragraph 12 of the previous Office action is withdrawn because the Deacon et al article is no longer prior art against the instant claims, and because the WO Patent Application 95/15309 does not teach or suggest oral administration of its DPIV inhibitors.

It should be noted that even in view of corrected claim for priority, the Balkan et al abstract (Diabetologia, Suppl. 40, A131 Abstract) remains available as prior art against Applicants' claims. Accordingly, the obviousness rejection set forth in paragraph 13 of the previous Office action, which relied upon the Deacon et al article and the Balkan et al abstract in the alternative to one another, is maintained.

The rejection based upon Villhauer (U.S. Patent No. 6,011,155) is maintained. U.S. patents are presumed operable and enabled, with the burden being upon Applicants to provide evidence of inoperability or lack of enablement. See MPEP 716.07 and 2121. Applicants' attorney's remarks do not satisfy this burden. Further, in vivo testing is not a requirement for enablement, and thus the possible lack of in vivo testing in Villhauer does not establish lack of

enablement. None of the rejected claims require the protease inhibitors to comprise a modified prolyl residue, nor do they specify what substituents can be attached to a modified prolyl residue. The cyano group present in the inhibitors of Villhauer is embraced by the rejected claims. Villhauer teaches single daily oral dosages at column 10, lines 41-42. With respect to Appendix III of Applicants' response, the examiner can find no indication that the article is by Villhauer or that the article discusses Villhauer's patent, nor can the examiner find any indication as to when and/or where the article was published. Page 5 of Appendix III discusses two to three times daily administration of an inhibitor developed by Novartis, and cites to footnote 49. However, the article in footnote 49 is not authored by Villhauer. Appendix III does not contradict the actual teaching in Villhauer of once-daily administration.

The rejection based upon the German Patent '486 is maintained. Examples are not a prerequisite for enablement. The rejected claims do not require a protease inhibitor which forms a covalent complex with DPIV, nor do they exclude protease inhibitors which are quickly cleared from circulation. Patentability must be based upon claimed, not unclaimed, differences over the prior art.

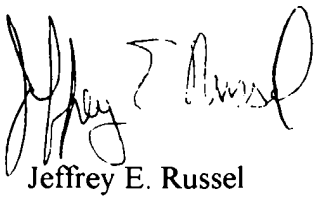
13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

November 6, 2003